

## Environmental Chemicals and Nervous System Dysfunction<sup>1</sup>

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Selected examples of associations between nervous system diseases and exposures to occupational and environmental chemicals have been reviewed. Recent outbreaks of human neurotoxicity from both well-known and previously unknown toxicants reemphasize the need for the medical community to give increased attention to chemical causes of nervous system dysfunction.

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### INTRODUCTION

We live in a world of chemicals. The Chemical Abstracts Service's unique computer registry of chemicals contained over 4 million distinct chemical entities as of November 1977 [1]. Although a majority of these chemicals are isolated from natural products or synthesized in small quantities only for research purposes, many are produced for widespread commercial usage, particularly as pharmaceutical, agricultural, and industrial chemicals. Each year 500-1,000 new compounds are produced in commercial quantities. It has been predicted that the initial inventory (to be compiled by the Environmental Protection Agency under the 1976 Toxic Substances Control Act) of chemical substances manufactured, imported, or processed in the United States since January 1975 may include as many as 70,000 chemicals. Although many of these compounds are probably not harmful, we will inevitably be exposed to some of them. Many of these industrial chemicals may enter the environment as waste products discharged into the air, rivers, and lakes, and some will eventually find their way into humans through contaminated food, water, and air. A few have found their way into the food chain through accidental contamination due to carelessness or ignorance and these have been responsible for serious localized outbreaks of human poisoning. Another widespread and primary source of human contact is occupational exposure to specific chemicals found in industrial and commercial environments. Occupational exposure often provides an early warning of potential hazards in the general environment.

Unfortunately, only a few chemicals have been adequately examined for their effects on human health, particularly with respect to the more subtle, subclinical

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TABLE 1  
Nervous System Diseases and Associated Chemicals

<i>Autonomic Nervous System</i>	
Autonomic dysfunction:	acrylamide; carbon disulfide; organo-phosphate esters; thallium; mercury
<i>Central Nervous System</i>	
Mental retardation:	carbon monoxide; dichloroethane; lead; methylmercury
Brain edema:	hexachlorophene; methyl bromide; triethyltin
Cerebrovascular arteriosclerosis:	carbon disulfide
Dementia, presenile:	aluminum; carbon disulfide; methylmercury
Encephalitis:	lead; methylmercury; thallium; arsine; toluene
Demyelination (multifocal):	hexachlorophene; triethyltin; tetraethyl lead
<i>Peripheral Nervous System</i>	
Facial paralysis:	trichloroethylene
Optic neuritis:	carbon disulfide; cyanide; thallium
Polyneuritis:	Alkyl and aryl phosphates; Leptophos; Kepone; DDT; acrylamide; n-hexane; methyl-n-butyl ketone; arsenic; lead; methylmercury; thallium; tellurium; carbon monoxide; carbon disulfide; carbon tetrachloride; 2,4-dichlorophenoxyacetic acid; hexachlorophene; methyl bromide; methyl chloride; phthalate esters

effects that may result from chronic low-level exposures. The nervous system may be particularly vulnerable to many of these exogenous chemicals.<sup>1</sup> Selective damage to particular areas of the nervous system has been noted with numerous toxins, and certain groups, such as the young and the elderly, may be especially vulnerable.

An ongoing activity of the Office of Health Hazard Assessment at the National Institute of Environmental Health Sciences is to create and maintain an open-ended data file of associations between environmental chemicals and target organ diseases, symptoms, and signs. This review gives some selected examples of neurotoxic effects associated with exposure to environmental and occupational chemicals.

### TYPES OF NEUROTOXIC EFFECTS

Tables 1–3, represent an abbreviated compilation of reported associations between human nervous system diseases (Table 1), neurological manifestations (Table 2), behavioral symptoms (Table 3), and exposure to environmental and occupational chemicals. Literature references will be given when some of these associations are discussed in greater detail. In some instances, cause and effect relationships have been clearly established, while the evidence for other associations is limited to a few case reports. The tables are not intended to be complete, inclusive catalogs of either nervous system symptoms or neurotoxic chemicals, but rather to illustrate the diverse and multiple effects that may be produced by neurotoxic compounds. The terms used to describe the nervous system diseases and symptoms were chosen because they appear as official medical subject headings in the National Laboratory of Medicine's

<sup>1</sup> Unfortunately, a standardized battery of sensitive screening tests for detecting and predicting the neurotoxic effects of chemicals does not exist at the present time.

TABLE 2  
Neurological Manifestations and Associated Chemicals

<i>Movement Disorders</i>	
Ataxia:	acrylamide; methylmercury; lead; carbon monoxide; cyanide; dichloroethane; methyl chloride; organo-phosphate esters; Kepone
Myoclonus:	methylmercury; thallium; dichloroethane; methyl bromide
Parkinsonism:	manganese
Tic (facial):	mercury; trichloroethylene
Tremor:	acrylamide; aniline; lead; manganese; mercury; ethylene dichloride; Kepone; DDT; Chlordane; Leptophos
Pathological reflexes:	acrylamide; hexachlorophene; n-hexane; methyl-n-butyl ketone; lead; sulfur dioxide; toluene
<i>Sensation Disorders</i>	
Anosmia:	cadmium; carbon disulfide; sulfur dioxide
Hyperesthesia:	arsenic
Paresthesia:	acrylamide; arsine; lead; manganese; methylmercury cyanide; carbon disulfide; n-hexane; methyl-n-butyl ketone; organo-phosphate esters
<i>Sleep Disorders</i>	
Hypersomnia:	acrylamide; manganese; dichloroethane
Insomnia:	ethylene dichloride; carbon disulfide; tetraethyl lead; mercury; organo-phosphate esters
<i>Speech Disorders</i>	
(slurring of speech, stuttering, dysarthria):	acrylamide; benzene; methyl bromide; methyl chloride; methylmercury; phenylmercury; manganese; organo-phosphate esters; Kepone
<i>Hearing Disorders</i>	
Hearing loss:	cyanide; lead; methylmercury
Tinnitus:	aniline; cyanide; toluene; organo-phosphate esters
<i>Vision Disorders</i>	
Amblyopia:	mercury; phenylmercury; cyanide; 2,3,7,8-tetrachlorodibenzo-p-dioxin; organo-phosphate esters
Diplopia:	hexachlorophene; methyl bromide; methyl chloride
Nystagmus:	ethylene dichloride; thallium; organo-phosphate esters
Pupil reactions (abnormal):	methylmercury; lead; thallium; organo-phosphate esters

*Index Medicus.* The use of these terms facilitates the computerized, on-line retrieval of bibliographic citations from the Medline<sup>2</sup> and Toxline<sup>3</sup> data bases.

It is apparent from these tables, that the actions of toxic agents on both the central and peripheral nervous system are extremely varied and complex, and reflect a variety of physiological and biochemical mechanisms. The compounds associated with nervous system disorders include many different chemical structures and are widely employed in a variety of commercial and industrial processes. All structures of the nervous system may be affected, though certain anatomical areas and cell types

<sup>2</sup>Medical Literature Analysis and Retrieval System on-Line, a data base maintained by the National Library of Medicine containing bibliographic citations from biomedical journals.

<sup>3</sup>Toxicology Information on-Line, a data base maintained by the National Library of Medicine containing references to published human and animal toxicity studies.

TABLE 3  
Behavioral Symptoms and Associated Chemicals

<i>Affective Disturbances</i>	
Euphoria/Excitement:	toluene; manganese; DDT; diethyl ether; n-hexane
Nervousness/Irritability:	benzene; chloroprene; 2,3,7,8-tetrachlorodibenzo-p-dioxin; ethylene dichloride; organo-phosphate esters; Kepone
Depression/Anxiety:	carbon disulfide; organo-phosphate esters; mercury; carbon tetrachloride; lead; Kepone
Psychoses:	organo-phosphate esters; carbon disulfide
<i>Cognition Disorders</i>	
Mental confusion:	chloroprene; toluene; methyl bromide; methyl chloride; carbon tetrachloride; adiponitrile; methylmercury; Kepone
Delirium/Hallucinations:	thallium; toluene; methyl chloride; dimethyl-sulphate; acrylamide; manganese; hydroquinone
Memory disorders:	manganese; toluene; methyl chloride; ethylene dichloride; organo-phosphate esters; Kepone

appear to be more vulnerable. Some compounds act directly on the nervous system, whereas others affect nonneuronal processes which in turn affect the nervous system. More generalized neurotoxic effects may result from such processes as anoxia or protein denaturation. Other neurotoxins interfere with more specific biochemical mechanisms. In most instances, the mechanisms of human neurotoxicity remain undefined. Peripheral neuropathy is a consequence of exposure to many chemicals, but frequently mixed central and peripheral nervous system effects are involved. Nervous system tumors are not listed in Table 1, since there is little concrete data for the environmental induction of these tumors in humans, though they can be produced in animal studies by such compounds as nitrosoalkylureas and triazenes. Ultimately, direct or indirect damage to the nervous system will result in functional disturbances. Tables 2 and 3 show that sensory and motor functions, cognitive processes such as learning and memory, arousal mechanisms, and emotional factors may all be affected.

Unfortunately, many of the neurological and behavioral symptoms listed in Tables 2 and 3 are considered subjective, minor, or nonspecific, and can readily be attributed to a number of other factors. It is therefore difficult to correlate such symptoms with chemical causes unless some preliminary warning of the possible hazard has been given. Nevertheless, such symptoms cannot be disregarded, since subtle changes in nervous system function may precede the more overt symptoms of intoxication and histopathological damage. Even though functional correlates of neurotoxicity are not easily determined and are seldom specific (just as correlates of fever, oxygen deficiency, or gastrointestinal disturbances are nonspecific), combinations of nonspecific changes can lead to an elucidation of "syndromes" typical for a chemical or a group of chemicals. The neurotoxicology of a few compounds listed in Tables 1-3 is discussed in greater detail. Effects on other organ systems and their interrelationships with the nervous system, though important, are not emphasized here.

### INORGANIC AND ORGANO-LEAD COMPOUNDS

The neurotoxicity of inorganic lead at high doses has been well documented for many decades. Although the occurrence of severe lead poisoning in children and

adults is diminishing, classic symptoms of lead intoxication are still reported in young children who chew on lead-painted objects [2,3]; in adults after the ingestion of contaminated illicit whiskey [4-6]; and in occupationally exposed workers [5]. Encephalopathy is one of the most serious consequences of acute lead intoxication, since permanent damage often occurs, particularly in young children [7-12]. Other neurological symptoms following acute lead exposure include tremors, disorientation, neuropathy, aphasia, blindness, convulsions, and coma [13]. The neuropathy is primarily a motor neuropathy, which usually shows up as wrist drop and/or foot drop paralysis. Histologically, adults develop primary changes in the Schwann cells with segmental disintegration beginning at the nodes of Ranvier [14,15]. Animal studies have shown that lead produces segmental demyelination [16-18], but this has not yet been shown concretely in humans. Peripheral neuropathy is rarely reported in lead intoxicated children, but Feldman et al. [19] suggest that childhood neuropathy may be overshadowed by the clinical symptoms of encephalopathy. They found reduced motor nerve conduction velocities in children with a known history of plumbism. More recently, it was reported that children with sickle cell disease may be predisposed to the development of lead neuropathy [20,21]. Children with sickle cell disease displayed motor weakness, reflex abnormalities, mild hypesthesia, and reduced nerve conduction velocities subsequent to lead intoxication.

The possibility that continuous exposure to low levels of lead may have subtle neurological and behavioral effects is a growing concern. Indications of subclinical peripheral neuropathy were reported by Seppäläinen et al. [22]. They observed impaired motor nerve conduction velocities in otherwise neurologically asymptomatic workers whose blood lead levels had not exceeded 70  $\mu\text{g}/100\text{ ml}$ . Recently, Lilis et al. [23] found that lead exposed workers, whose blood lead levels were lower than 80  $\mu\text{g}/100\text{ ml}$  and who had no history of higher blood lead concentrations, had an increased incidence of such central nervous system symptoms as irritability and sleep disturbances. However, nerve conduction velocities did not differ significantly from the controls. It has also been a concern that chronic, asymptomatic lead exposure may cause subtle behavioral and neurological impairment in young children. An association between lead exposure and childhood hyperactivity was suggested by David et al. [24]. However, it cannot be ruled out that lead absorption was secondary to hyperactivity since disturbed children tend to exhibit an increased incidence of pica [25,26]. The statistical treatment of this study has also been criticized [27]. Many studies suggest an association of asymptomatic lead exposure with mental and behavioral impairment [28-32]; but other studies have not found such an association [33-36]. Thus the data presently available are conflicting and inadequate to conclude that subtle psychological, emotional, and neurological damage occurs in children as a result of lead exposure at levels below those causing clinical symptoms. Resolution of this matter is of considerable importance.

The clinical picture of intoxication due to organo-lead compounds such as tetraethyl lead, is quite different from that produced by inorganic lead compounds. Tetraethyl lead can be absorbed rapidly through the skin, is soluble in central nervous system structures, and is demethylated by liver microsomes to triethyl lead, which is presumably the toxic metabolite [37]. Neurological symptoms resulting from tetraethyl lead exposure range from euphoria, nervousness, insomnia, and excessive daydreaming to hallucinations and acute psychoses, depending upon the severity and duration of exposure [38]. These symptoms are generally reversible. Animal studies indicate that triethyl lead is a multifocal central nervous system hypomyelinating agent [39].

## ELEMENTAL, INORGANIC AND ORGANO-MERCURY COMPOUNDS

Inhalation of elemental mercury vapors can lead to such neurological symptoms as slight tremor, amblyopia, insomnia, anxiety, depression, and autonomic nervous system dysfunction [40]. Similar neurological symptoms may also result from chronic exposure to inorganic mercury salts, but these compounds are less able to penetrate the central nervous system and appear to exert their primary effect on the kidney [41].

Exposure to organo-mercury compounds, particularly methylmercury, can result in severe, irreversible damage to the central nervous system. Thousands of cases of methylmercury intoxication were reported in Iraq in 1971–1972, when seed grain treated with mercury-containing fungicides, was inadvertently used to make bread [42]. Another major outbreak occurred in Japan, where mercury-containing wastes, discharged into the waters of Minamata Bay, resulted in high methylmercury concentrations in fish, and in the subsequent poisoning (Minamata disease) of fish-eating families [43]. Unfortunately, methylmercury has become a fairly ubiquitous pollutant. For example, certain populations in Canada and Sweden continue to be exposed to methylmercury through the consumption of contaminated game fish caught in waters polluted with mercury effluents from chloralkali plants and paper mills [44–46].

The initial symptoms of methylmercury intoxication are primarily neurological and behavioral, and include paresthesia, astereognosis, hearing and vision disorders, cerebellar ataxia and dysarthria, myoclonus, irritability, and memory impairment [47–49]. Some of these symptoms are reversible, depending upon the degree of exposure. The sensory deficits generally appear first. Constriction of the visual field is the most common visual deficit, and it may be one of the earliest signs of chronic methylmercury exposure in primates [50]. The motor disturbances range from impairment of fine motor control to cerebellar ataxia and dysarthria. Methylmercury causes a distinctive spread of necrosis in the granule cell layer of the cerebellar cortex and visual cerebral cortex [48]. Clinical electrophysiological studies have not revealed firm evidence of peripheral neuropathy [51]. The duration and timing of exposure are critical variables. Methylmercury can easily cross the placenta, and fetal and neonatal exposure (via breast milk) can result in irreversible, severe neurological defects, including mental retardation, blindness, and deafness [52].

## KEPONE

It has been known for years that acute and chronic exposure to chlorinated hydrocarbon pesticides can affect the human nervous system. The recent dramatic example of human kepone intoxication reemphasizes the need for continuing surveillance of the health effects of these compounds. Kepone (common name, Chlordecone), a complex polychlorinated hydrocarbon pesticide, had been manufactured in very small quantities in the United States until 1974, when a small factory in Virginia began its mass production. More than a hundred workers were heavily exposed, and some of their spouses and children also showed evidence of exposure. This chemical has also polluted some Virginia waterways [53].

The workers exposed to kepone suffered severe neurological and behavioral impairment in addition to mild liver disorders and decreased sperm production [54]. The neurological symptoms included tremors, slurred speech and stuttering, opsoclonus, exaggerated startle response, and signs of cerebellar dysfunction (incoordination and gait ataxia). Behavioral symptoms included anxiety, irritability, memory disturbances, and hyperkinesia. Clinical symptoms of a peripheral neuropathy were

generally not apparent and motor nerve conduction velocities were within the normal range [55]. Histopathological studies of peripheral nerves revealed damage primarily to the nonmyelinated and smaller myelinated nerve fibers, and suggested primary involvement of the Schwann cells [56]. The severity of the neurological and behavioral symptoms appears to be directly related to the degree and duration of exposure. Symptoms may begin as early as a week after exposure, and have not always improved after termination of exposure. Fortunately, it has recently been shown that treatment with the drug, cholestyramine, hastens the excretion of kepone and decreases the severity of the symptoms [57].

### ORGANO-PHOSPHATES

Organo-phosphorus (OP) esters are widely used as pesticides, and have substantially replaced many of the more persistent chlorinated hydrocarbon insecticides. Although most organo-phosphates are rapidly hydrolyzed and have few cumulative ecological effects, they do produce acute toxic effects and have frequently caused accidental fatalities in both humans and in domestic animals [58]. The toxicity is mainly due to cholinesterase inhibition, resulting in excessive muscarinic and nicotinic effects [59]. The central nervous system symptoms of OP intoxication include convulsions, speech disorders, insomnia, drowsiness, coma, anxiety, irritability, depression, impaired memory, and personality disorders [60,61]. These vary in severity, rapidity of onset, and duration depending upon the particular OP compound involved. Signs of intoxication are usually not apparent until the levels of acetylcholinesterase have been reduced by at least 50%, because adaptation to low cholinesterase levels can occur. After recovery from acute OP poisoning, certain central nervous system effects, such as impaired memory, depression, and electroencephalographic changes may persist for weeks or months [62,63]. Concern has also been raised that chronic occupational exposure to OP compounds may result in subclinical, neurological and behavioral deficits. Abnormal electroencephalograms, anxiety, depression, and impaired memory have been reported in otherwise asymptomatic agricultural and industrial workers [64-67]. Other studies, however, have been negative [68,69] and more data are necessary to resolve this important issue.

In addition to the central nervous system cholinergic effects, a small group of the organo-phosphorus compounds produce degenerative changes in the central and peripheral nervous system which ultimately result in a sensory-motor neuropathy. This neuropathy does not manifest itself until several days or weeks after exposure. This delayed neuropathy is not primarily a function of the central cholinergic response, since most OP compounds do not cause delayed neuropathy. Once exposure has occurred there is presently no way of preventing the development of the neuropathy. Attention was first focused on the delayed neurotoxicity syndrome in the United States in 1930 [70] when more than 20,000 humans developed paralysis after accidental exposure to triorthocresyl phosphate (TOCP), an aryl phosphate used as a lubricant and plasticizer. A second outbreak of TOCP neuropathy and paralysis, also involving thousands of people, occurred in Morocco in 1959 [71]. Accidental exposure to the pesticides, Mipafox [72], Merphos [73], and possibly Leptophos [74], have also resulted in some cases of delayed neuropathy in humans.

The OP delayed neurotoxicity syndrome begins one to three weeks after exposure. Initial symptoms include paresthesia, hypesthesia, abnormal reflexes, and muscle weakness [75,76]. Muscle weakness begins in the feet and spreads progressively to the legs, hands, and forearms. Mild cases usually recover, but in severe cases ataxia, and permanent paralysis can occur. Sensory and motor nerves, the spinal cord, and

medulla oblongata may all be damaged [78]. An accumulation of membrane-bound vesicles within the axoplasm of motor and nerve terminals, as well as distal, secondary demyelination have been observed [77,78]. Recent studies have shown that the delayed neuropathy-inducing OP compounds interfere in a specific way with a characteristic membrane-bound nerve cell protein, referred to as "neurotoxic esterase" [79–82]. The precise mechanisms involved in the delayed neurotoxicity syndrome have not been determined.

### n-HEXANE AND METHYL-n-BUTYL KETONE

Although most organic solvents are known to be central nervous system depressants at high concentrations, they have generally been considered to be relatively non-neurotoxic at low concentrations. Recently, however, several outbreaks of sensorimotor neuropathy have been reported as a result of prolonged exposure to relatively low levels of n-hexane and methyl-n-butyl ketone (MBK). Neuropathy due to n-hexane (a solvent used in many industrial processes, often a major component of glues, and a minor component of petroleum) has been reported in glue sniffers [83–86], in shoe-industry workers [87,88], cabinet refinishers [89], and in makers of adhesive products [90]. The neurological symptoms include paresthesia, reflex loss, symmetrical distal ascending motor weakness, and an unsteady gait [87–90]. There is a slowing of sensory and motor nerve conduction velocities, usually proportional to the severity of the clinical deficits. In glue sniffers, motor impairment tends to be more severe and muscle biopsies have shown neurogenic atrophy [83–86]. A similar sensorimotor neuropathy has recently been reported in workers exposed to the widely used solvent and cleaning agent, methyl-n-butyl ketone [91–95]. Clinical symptoms again included paresthesia, mild reflex loss, progressive symmetrical distal muscle weakness, and a slowing of motor nerve conduction velocities [91–94]. The symptoms of n-hexane and MBK neuropathy are usually reversible, but recovery is often slow.

Animal studies and human nerve biopsies have shown that n-hexane and MBK cause axonal degeneration in the distal parts of vulnerable nerves. This axonal degeneration is accompanied by a characteristic pattern of histopathological changes [83,85,96,97]. These changes consist of multiple and focal, giant axonal swellings displaying an accumulation of 10 nm neurofilaments. Neurofilament accumulation occurs first in myelinated axons, where the swellings occur on the proximal, distal sides of the nodes of Ranvier, but similar changes eventually occur in nonmyelinated axons. Schaumborg and Spencer [98,99] have shown that these changes occur concomitantly in both the central and peripheral nervous system. An accumulation of neurofilaments within axons has also been observed in acrylamide-induced neuropathy [100,101].

The mechanisms of axonal degeneration are unknown, but similar histopathological changes [102,103] have been observed with 2,5-hexanedione, a metabolite of both n-hexane and MBK [104,105], which suggests that there may be a common metabolic basis for the neuropathy induced by n-hexane and MBK.

### COMMENTS

The etiology of many neurological and/or psychiatric disorders is obscure or completely unknown. Affected patients frequently have nonspecific complaints that are easily passed off as being minor, temporary, psychosomatic, due to stress, etc. However, these same subtle symptoms may be the first signs of intoxication with



environmental and occupational chemicals. The medical community should become sensitized to considering nervous system toxicants as a source of these otherwise unexplainable symptoms, and evidence for occupational and environmental exposures must be included in the differential diagnosis of neurological diseases.

The toxicity of the compounds mentioned in this review is now well known, but they may represent only the "tip of the iceberg." The Toxic Substances Control Act of 1976 requires that new compounds be properly tested so that their health effects can be evaluated before human exposure occurs. The continued alertness of the medical community to the potential chemical causes of nervous system dysfunction is necessary to insure that this legislation becomes effective.

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